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1: Biochemistry. 1993 Jun 29;32(25):6485-92.

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The divalent cation is obligatory for the binding of ligands to the catalytic site of secreted phospholipase A2.

Yu BZ, Berg OG, Jain MK.

Department of Chemistry and Biochemistry, University of Delaware, Newark 19716.

The divalent cation requirement for partial reactions of the catalytic turnover cycle during interfacial catalysis by pig pancreatic phospholipase A2 (PLA2) is investigated. Results show that the specific role of calcium in all the events of the catalytic cycle at the active site is not shared by other divalent cations. Cations such as calcium, barium, and cadmium bind to the enzyme in the aqueous phase. The active-site-directed ligands (substrate, products, and transition-state mimics) do not bind to the enzyme in the absence of a divalent cation. The synergistic binding of such ligands to the active site of PLA2 bound to the interface is, however, observed only in the presence of isosteric ions like calcium and cadmium, but not with larger ions like strontium or barium. The equilibrium constants for ligands bound to the enzyme in the presence of calcium and cadmium are virtually the same. However, only calcium supports the catalytic turnover; the rate of hydrolysis in the presence of cadmium is less than 1% of that observed with calcium. The role of divalent ions on the interfacial catalytic turnover cycle of PLA2 is not only due to the cation-assisted binding of the substrate but also due to its participation in the chemical step. Other roles of divalent ions in the events of interfacial catalytic turnover are also identified. For example, the binding of the enzyme to the interface is apparently promoted because the divalent cation is required for the sequential step, i.e., the binding of the substrate to the active site of PLA2. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 8518290 [PubMed - indexed for MEDLINE]

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1: Biochim Biophys Acta. 1993 Apr 23;1167(3):272-80.

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Metal ion and salt effects on the phospholipase A2, lysophospholipase, and transacylase activities of human cytosolic phospholipase A2.

Reynolds LJ, Hughes LL, Louis AI, Kramer RM, Dennis EA.

Department of Chemistry, University of California, San Diego, La Jolla 92093-0601.

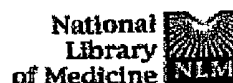
Human cytosolic phospholipase A2 (cPLA2) is an arachidonic acid specific enzyme which may play a role in arachidonic acid release, eicosanoid production, and signal transduction. The PLA2 activity of this enzyme is stimulated by microM levels of Ca2+. Using a pure recombinant enzyme, we have confirmed that cPLA2 is not absolutely dependent on Ca2+, since Sr2+, Ba2+ and Mn2+ also gave full enzyme activity. Heavy metals, in contrast, inhibited enzyme catalysis suggesting the involvement of an essential cysteine residue. In the absence of Ca2+, high salt concentrations overcame the requirement for divalent metals, indicating that Ca2+ is not required for PLA2 catalytic activity. cPLA2 also displays a lysophospholipase (lyso PLA) activity with lysophosphatidylcholine micelles as a substrate. Unlike the PLA2 activity, the lyso PLA activity toward these micelles is not stimulated by Ca2+. However, upon the addition of glycerol or Triton X-100 to the assay, Ca2+ activation is observed, indicating that substrate presentation can affect the apparent Ca2+ dependence. Glycerol was found to be a potent stimulator of lyso PLA activity and specific activities up to 50 mumol min-1 mg-1 were observed. In addition to the PLA2 and lyso PLA activities, we report that cPLA2 displays a relatively low, CoA-independent transacylase activity which produces phosphatidylcholine from lysophosphatidylcholine substrate. The observation of this novel transacylase activity is consistent with the formation of an acyl-enzyme intermediate.

PMID: 8481388 [PubMed - indexed for MEDLINE]

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1: J Biol Chem. 1990 Jun 5;265(16):9201-7.

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Divalent cation regulation of phosphoinositide metabolism. Naturally occurring B lymphoblasts contain a Mg²⁺-regulated phosphatidylinositol-specific phospholipase C.

Chien MM, Cambier JC.

Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206.

Membranes isolated from normal murine B lymphocytes were found to contain a novel phosphatidylinositol (PtdIns)-specific phospholipase C (PLC) which becomes activated as the Mg²⁺ concentration is raised from 30 to 1000 microM. This activity, which has not been described previously in any tissue, is restricted to naturally occurring B cell blasts, i.e. it was not detected in quiescent B cells, B lymphomas, or plasmacytomas. As seen in other cell systems, B cell membranes were found to contain Mg²⁺-stimulated inositol 1,4,5-trisphosphate phosphatase activity. Although neither the inositol 1,4,5-trisphosphate phosphatase nor the PtdIns PLC activities were affected by Ca²⁺, B cell membranes were found to contain a Ca²⁺-stimulated phosphatidylinositol 4,5-bisphosphate (PtdInsP₂) PLC activity which is activated by [Ca²⁺] greater than 100 nM. Based on several characteristics, it appears that the Mg²⁺- and Ca²⁺-regulated PLCs are distinct species. First, they have distinct specificity for PtdIns and PtdInsP₂, respectively. Second, they have distinct tissue distribution while the Ca²⁺-regulated activity was detected in all B cells, the Mg²⁺-regulated activity is restricted to low density, natural B blasts. Third, the kinetics of activation of the enzymes is distinct; the Mg²⁺-regulated enzyme exhibits slower and less transient activation kinetics. Fourth, the activities exhibit absolute specificity in terms of activation by Mg²⁺ and Ca²⁺, i.e. the PtdIns PLC is activated only by Mg²⁺ and the PtdInsP₂ PLC is activated only by Ca²⁺. Data are consistent with the possibility that Mg²⁺ mobilization which follows ligation of certain receptors, may play an important role in the regulation of levels of the second messenger diacylglycerol.

PMID: 2160965 [PubMed - indexed for MEDLINE]

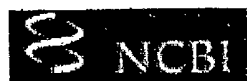
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1: Biochemistry. 1998 Sep 8;37(36):12576-87.

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Catalytic significance of the specificity of divalent cations as KS* and kcat* cofactors for secreted phospholipase A2.

Yu BZ, Rogers J, Nicol GR, Theopold KH, Seshadri K, Vishweshwara S, Jain MK.

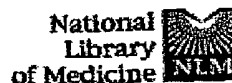
Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, USA.

Calcium is required for the substrate binding and for the chemical step of the interfacial catalytic turnover cycle of pancreatic phospholipase A2 (PLA2), but not for the binding of the enzyme to the interface. The role of calcium and other divalent cations (C) is analyzed for the effect on the substrate binding and kcat* for the chemical step. The cofactor role of 3d-cations(II) (C) for the hydrolysis of dimyristoylphosphatidylmethanol (DMPM) vesicles is characterized as an equilibrium dissociation constant for the interfacial binary (E*C) and ternary (E*CL) complexes of PLA2 and substrate mimics (L). Of the cations(II) that promote the binding of a mimic to the enzyme at the interface (E*), only a subgroup supports the chemical step. For example, Cd, Zn, and Cu form ternary E*CL complexes with kcat* of <1 s-1, compared to the rate of >100 s-1 with Ca, Fe, Mn, Co, and Ni. Oxygen exchange from H218O to the products of hydrolysis of DMPM incorporates one 18O in myristate. Incorporation of the first and second 18O occurs during the incubation of both the products of hydrolysis in H218O with PLA2 and Ca, but not with Zn. The cation-dependent changes in the UV difference spectrum, associated with the formation of E*C and E*CL, suggest that the changes are mainly due to catalytic His-48, and possibly Tyr-52 and Tyr-73, and are different with Ca as opposed to Zn. These results and simulations suggest considerable plasticity in the calcium binding and catalytic site environment. It is proposed that the higher ground state stability of the E*CS complex with the inhibitory cations increases the effective activation energy. For the chemical step, calcium coordinated with a nucleophilic water and the ester carbonyl oxygen facilitates the near-attack geometry in the E*CaS, and the His-48.Asp-99 pair acts as a proton acceptor. As a prelude to establishing the catalytic mechanism, factors controlling the energetically demanding transition state are also discussed.

PMID: 9730830 [PubMed - indexed for MEDLINE]

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1: Inflammation. 1996 Dec;20(6):599-611.

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Zinc (Zn²⁺) binds to and stimulates the activity of group I but not group II phospholipase A2.

Lindahl M, Tagesson C.

Department of Occupational and Environmental Medicine, University of Linköping,
 Faculty of Health Sciences, Sweden.

Phospholipase A2 plays an important part in the generation of inflammatory lipid mediators and so it is of major interest to understand functional distinctions between structurally similar forms of phospholipase A2. In the present study, the influence of zinc (Zn²⁺) on the activity of group I and group II phospholipase A2 was examined in vitro. It appeared that Zn²⁺ (0.04-1 x 10⁻³M) increased group I phospholipase A2 activity from porcine pancreas and rat lung whereas the activity of group II phospholipase A2 from *Crotalus atrox* and *Vipera russelli* was unaffected. The presence of Cd²⁺ or Hg²⁺ (0.8-5 x 10⁻³M) also increased group I pancreatic phospholipase A2 activity while no augmentation was found with Cr²⁺, Fe²⁺ or Mg²⁺. The selective stimulation of group I phospholipase A2 by Zn²⁺ corresponded to a binding of these phospholipases A2 to a zinc-affinity column, while group II phospholipase A2 was not bound. Furthermore, the PLA2 activity in bronchoalveolar lavage fluid from rat was stimulated by Zn²⁺. These results indicate that Zn²⁺ binds to and increases the activity of group I, but not group II phospholipase A2. This difference in Zn(2+)-binding may be used to discriminate between group I and group II phospholipase A2 and to separate the enzymes from each other in complex biological materials. The possibility that activation of group I phospholipase A2 in the lung is important in zinc-induced metal fume fever is implied.

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